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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/824,468	04/02/2001	Arthur M. Krieg	C1039/7049(HCL/MAT)	9046

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EXAMINER
GIBBS, TERRA C

ART UNIT	PAPER NUMBER
1635	9

DATE MAILED: 10/03/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/824,468	Applicant(s) KRIEG ET AL.	
	Examiner Terra Gibbs	Art Unit 1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 April 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *22-43* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *22-43* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Preliminary Amendment A, filed on 4/2/01, in Paper No. 4 requests to cancel claims 1-20. Renumbered claim 1-21 m 9/2/02 ~~Claims 1-20~~, have been canceled.

The numbering of claims is not in accordance with 37 CFR 1.126 which requires the original numbering of the claims to be preserved throughout the prosecution. When claims are canceled, the remaining claims must not be renumbered. When new claims are presented, they must be numbered consecutively beginning with the number next following the highest numbered claims previously presented (whether entered or not). Submitted claims 21-42 have been renumbered 22-43.

Claims 22-43 are pending in the instant application.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 22-31 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims read on a method for stimulating a synergistic immune response in a subject comprising the administration of a combination of an immunostimulatory CpG oligonucleotide

and a cytokine selected from the group consisting of IL-3, IL-5 and IL-12 for inducing a synergistic antigen specific immune response.

The scope of the claimed invention encompasses a genus of antigen specific immune responses that are not described in the specification as filed. Revised Interim Guidelines state, "The claimed invention as a whole may not be adequately described if the claims require an essential or critical element which is not adequately described in the specification and which is not conventional in the art" (Column 3, page 714334). In the instant case, a description of a "synergistic antigen specific immune response" is a critical element for each species of the claimed invention because a synergistic antigen specific immune response can occur in *any* cell of an organism. Therefore, in order to meet the written description requirement according to the full scope of the claimed invention, applicant must provide a description of a "synergistic antigen specific immune response" according to the definition provided in the instant application. The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species, by actual reduction to practice, reduction to drawings, or by disclosure of relevant identifying characteristics (see MPEP 2163(ii)). The specification does not provide a definition of a synergistic antigen specific immune response, which is reduced to practice. The specification fails to teach the characteristics of a synergistic antigen specific immune response, or the common attribution of the genus of all synergistic antigen specific immune responses.

In view of these considerations, a skilled artisan would not have viewed the teachings of the specification as sufficient to show that the applicant was in possession of the claimed invention commensurate to its scope because it does not provide adequate written description for

the broad class of [any and all] synergistic antigen specific immune responses. Therefore, only the embodiments of the invention reduced to practice in the examples meet the written description provision of 35 U.S.C. §112, first paragraph.

Claims 22-43 are rejected under 35 U.S.C. 112, first paragraph, because the specification does not reasonably provide enablement for compositions or methods for stimulating a synergistic immune response in *any* subject comprising the administration of a combination of an immunostimulatory CpG oligonucleotide and a cytokine selected from the group consisting of IL-3, IL-5 and IL-12. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. The scope of claims 22-37 encompass compositions or methods for stimulating a synergistic immune response in *any* subject comprising the administration of a combination of an immunostimulatory CpG oligonucleotide and a cytokine selected from the group consisting of IL-3, IL-5 and IL-12. The scope of claims 38-43 encompass a method for treating and increasing survival time of *any* subject having *any* neoplastic disorder, comprising the administration of a combination of an immunostimulatory CpG oligonucleotide and a cytokine selected from the group consisting of IL-3, IL-5 and IL-12. Consequently, the examples set forth in the specification do not constitute support for the entire scope of claims 22-43, and, as a result, the entire scope of claims 22-43 could not be supported without undue experimentation.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement

and whether any necessary experimentation is "undue." These factors include, but are not limited to:

(1) the breadth of the claims;
(2) the nature of the invention;
(3) the state of the prior art;
(4) the level of predictability in the art;
(5) the existence of working examples; and
(6) the quantity of experimentation needed to make or use the invention based on the content of the disclosure.

The above factors have been considered in determining that the specification does not enable the skilled artisan to make and/or use the invention. These factors, when considered together, illustrate that the art of CpG DNA is in its infancy and highly unpredictable. The discussion is also based on references whose teachings show that, despite a tremendous amount of experimentation by highly skilled artisans in the field of immunostimulatory properties of CpG oligonucleotides and gene therapy, there remain significant hurdles known in the art to make and/or use the invention claimed.

(1-2) The breadth of the claims and the nature of the invention: Claims 22-37 are drawn to compositions or methods for stimulating a synergistic immune response in a subject comprising the administration of a combination of an immunostimulatory CpG oligonucleotide and a cytokine selected from the group consisting of IL-3, IL-5 and IL-12. Claims 38-43 are drawn to a method for treating and increasing survival time of a subject having a neoplastic disorder, comprising the administration of a combination of an immunostimulatory CpG oligonucleotide and a cytokine selected from the group consisting of IL-3, IL-5 and IL-12. Such claims represent a broad scope because it reads on *any* subject and *any* immunostimulatory CpG oligonucleotide, where it is unpredictable to determine biological effects from one organism to another (see

below) and where immunostimulatory CpG oligonucleotides have been found to be antagonistic to IL-3 and IL-5 production (see below). Further regarding claims 38-43 read on *any* neoplastic disorder. Additionally, methods of targeting nucleic acids, like CpG oligonucleotides, into a subject (whole organism) fall into the broad area known as gene therapy methods. While delivery of nucleic acids in and of itself is not considered as therapy *per se*, delivery shares many of the obstacles recognized for the actual therapy methods because successful therapy methods are, for the most part, based on the ability to deliver exogenous nucleic acids to cells or tissues of interest.

(3-4) The state of the art and the level of predictability in the art: The state of the art does not provide adequate guidance for one of skill in the art to predict how to stimulate a synergistic immune response in *any* subject comprising the administration of a combination of *any* immunostimulatory CpG oligonucleotide and a cytokine selected from the group consisting of IL-3, IL-5 and IL-12. Broide et al. (Journal of Immunology, 1998 Vol.161:7054-7062) disclose that an immunostimulatory DNA containing a CpG motif significantly inhibited Th2 cytokines, IL-5 and IL-3 in mice (see Abstract). This disclosure shows an antagonist effect of immunostimulatory CpG motif sequences on IL-5 and IL-3. Kreig and Wagner (Immunology Today, 2000 Vol. 21 pages 521-526) disclose, "the magnitude of the cytokine response to CpG DNA is much greater in mouse cells than with human or monkey cells" (see page 524, second column). Weiner (Journal of Leukocyte Biology, 2000 Vol. 68 pages 455-463) discloses, "All CpG ODN are not alike, and more needs to be learned about the heterogeneous responses that occur based on host organism, cell subset, or CpG ODN sequence" (see page 461, last paragraph). Weiner further discloses that the effects of CpG ODN on T cells remains

controversial as some investigators have reported that CpG ODN has a direct effect on T cells, however their group [Weiner] has not been able to detect such an effect (see page 457, second column). Assertions such as those from Broide et al., Kreig and Wagner and Weiner appear to indicate that much work need to be done to determine the biological effects of CpG oligonucleotides in organisms and to elucidate the role of cytokines in inducing a synergistic immune response using a combination of an immunostimulatory CpG oligonucleotide, for example. Additionally, the following reference is cited herein to illustrate the state of the art of gene delivery. Branch (TIBS Vol. 23, February 1998) teaches that the *in vivo* (whole organism) application of nucleic acids is a highly unpredictable endeavor due to target accessibility and delivery issues (see entire text).

(5) The existence of working examples: The instant specification teaches the combination of GM-CSF and CpG phosphorothioated oligonucleotide 2006 shows synergy for increasing the expression of CD86 and CD40 molecule expression on dendritric cells (see Figure 9). The instant specification (at page 11) contemplates the use of many cytokines, including IL-3, IL-5 and IL-12 as inducers of immune response synergism in a subject in combination with a CpG oligonucleotide. However, the examples do not teach a correlation between GM-CSF and IL-3, IL-5 or IL-12 such that one would substitute IL-3, IL-5 and IL-2 with GM-SCF to induce a synergistic immune response in a subject a combination of an immunostimulatory CpG oligonucleotide. Apart from the disclosure of GM-SCF fusion protein, the specification fails to teach how the skilled artisan would use IL-3, IL-5 and IL-12 as an inducer of immune response synergism in a subject a combination of a CpG oligonucleotide. One skilled in the art would not accept on its face the examples given in the specification of the synergism elicited by CpG

phosphorothioated oligonucleotide 2006 and the cytokine GM-CSF as being correlative or representative of the induction of immune response synergism in a subject a combination of a CpG oligonucleotide and IL-3, IL-5 and IL-12 in view of the lack of guidance in the specification and known unpredictability associated with the *in vivo* delivery of nucleic acids in a whole organism.

(6) The quantity of experimentation needed to make or use the invention based on the content of the disclosure: The quantity of experimentation needed to make or use the claimed invention would be great. The biological effects of CpG in organisms is highly unpredictable (see above). Furthermore, immunostimulatory DNA containing a CpG motif inhibited IL-5 and IL-3 in mice (see above). Therefore, the quantity of experimentation required to practice the invention as claimed would require the *de novo* determination of immunostimulatory CpG oligonucleotides that induce a synergistic immune response in a subject comprising a combination of an immunostimulatory CpG oligonucleotide and a cytokine selected from the group consisting of IL-3, IL-5 and IL-12 would occur. Therefore, it is deemed that further research would be necessary to make or use the invention as claimed. Thus, due to the inadequacies of the instant disclosure, one of ordinary skill would not have a reasonable expectation of success and the practice of the full scope of the invention would require undue experimentation.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Terra C. Gibbs whose telephone number is (703) 306-3221. The examiner can normally be reached on M-F 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on (703) 308-0447. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 746-8693 for regular communications and (703) 872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

tcg
September 26, 2002